New Ways to Add Salt

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Consultant Renal Physician
60% of the human body is fluid\textsuperscript{1,2}

- **Extracellular fluid**: 1/3 total body water (14 L)
- **Intracellular fluid**: 2/3 total body water (28 L)
- **Intravascular fluid**: 1/4 ECF (3.5 L)
- **Interstitial fluid**: 3/4 ECF (10.5 L)

Total body water: 60% of total body weight (42 L)

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The intra and extracellular fluid compartments differ in their ionic composition.

Water balance is regulated by a feedback loop: water excess

- Ingestion of water
  - Total body water
  - Plasma osmolality
    - Cellular hydration
      - Thirst
        - Vasopressin secretion
          - Urine water excretion by the kidney
            - Water intake
              - Ingestion of water

Water balance is regulated by a feedback loop: water deficit¹

This system is sensitive to small changes in plasma osmolality

Plasma osmolality, plasma vasopressin concentration and urine osmolality are closely related

- Under normal physiological conditions:
  - Changes in vasopressin secretion maintain plasma osmolality within narrow limits
- When water intake is not adequate to supply the body’s needs
  - Plasma vasopressin concentration increases to retain water (antidiuresis)
    - This increases urine osmolality
  - When maximal antidiuresis is achieved, plasma osmolality may continue to increase, stimulating thirst

Why is hyponatraemia clinically important?

- Most common electrolyte disorder encountered in clinical practice\(^1\)
- Associated with increased morbidity and mortality\(^2-3\)
- Considerable healthcare burden
  - Increased length of stay\(^2,5,6\)
  - Increased direct medical costs\(^7\)
- Underdiagnosed and mismanaged\(^8\)

Hyponatraemia is a relatively common electrolyte disorder

<table>
<thead>
<tr>
<th>Electrolyte disorder</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hyponatraemia</strong></td>
<td></td>
</tr>
<tr>
<td>Mild (Serum [Na$^+$] &lt; 135 mmol/L)</td>
<td>15–22% of hospitalised patients&lt;sup&gt;1&lt;/sup&gt; Approximately 7% of ambulatory patients&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Moderate&lt;sup&gt;1&lt;/sup&gt; (Serum [Na$^+$] &lt; 130 mmol/L)</td>
<td>Up to 7% of hospitalised patients&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Severe&lt;sup&gt;2&lt;/sup&gt; (Serum [Na$^+$] ≤ 125 mmol/L)</td>
<td>Around 3% of patients&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Hyperkalaemia</strong></td>
<td>2–5% of patients&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Hypercalcaemia</strong></td>
<td>&lt; 1%; 15 cases per 100,000 person-year&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Hypotonic hyponatraemia is classified according to volume status

<table>
<thead>
<tr>
<th>Total body water (TBW)¹</th>
<th>Hypervolaemic hyponatraemia</th>
<th>Euvolaemic hyponatraemia</th>
<th>Hypovolaemic hyponatraemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>↑↑</td>
<td>↑</td>
<td>↓</td>
<td></td>
</tr>
<tr>
<td>Total body sodium¹</td>
<td>↑</td>
<td>↔</td>
<td>↓↓↓</td>
</tr>
<tr>
<td>Extracellular fluid (ECF) volume²</td>
<td>↑↑</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Present</td>
<td>Absent</td>
<td>Absent</td>
<td></td>
</tr>
<tr>
<td>Oedema²</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cause¹-³</td>
<td>Congestive heart failure, cirrhosis, nephrotic syndrome, renal failure (acute or chronic)</td>
<td>SIADH, glucocorticoid deficiency, hypothyroidism</td>
<td>Renal solute loss: Diuretic therapy, cerebral salt wasting, mineralocorticoid deficiency, salt wasting nephropathy</td>
</tr>
</tbody>
</table>

Frequency of clinical features varies between acute and chronic yponatraemia

<table>
<thead>
<tr>
<th></th>
<th>Acute</th>
<th>Chronic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (n)</td>
<td>14</td>
<td>52</td>
</tr>
<tr>
<td>Duration</td>
<td>&lt; 12 hrs</td>
<td>3 days</td>
</tr>
<tr>
<td>Plasma $[\text{Na}^+]$ (mmol/L)</td>
<td>$112 \pm 2$</td>
<td>$118 \pm 1$</td>
</tr>
<tr>
<td>Stupor or coma</td>
<td>100%</td>
<td>6%</td>
</tr>
<tr>
<td>Seizures</td>
<td>29%</td>
<td>4%</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>50%</td>
<td>6%</td>
</tr>
<tr>
<td>Hyponatraemia deaths</td>
<td>36%</td>
<td>0%</td>
</tr>
</tbody>
</table>

Neurological manifestations of symptomatic hyponatraemia vary\textsuperscript{1,2}

- Symptomatic but less impaired; usually chronic
  - Headache
  - Irritability
  - Nausea / vomiting
  - Mental slowing
  - Unstable gait / falls
  - Confusion / delirium
  - Disorientation

- Life-threatening; usually acute
  - Stupor / coma
  - Convulsions
  - Respiratory arrest

The degree of symptomatology is a surrogate for the duration of hyponatraemia.

There is a U-shaped relationship between admission serum $[\text{Na}^+]$ and in-hospital mortality$^1$

There is an increased length of hospital stay in hyponatraemic patients\(^1\)

Increased mortality after hospitalisation with mild, moderate and severe hyponatraemia

Risk of death 5 years following admission in hyponatraemic patients ([Na⁺] < 134 mmol/L), compared with normonatraemic patients

Hyponatraemia metabolically contributes to bone loss


**Normonatraemic**

\[ [Na^+] = 141 \text{ mmol/L} \]

**Hyponatraemic**

\[ [Na^+] = 110 \text{ mmol/L} \]

Loss of cortical and trabecular bone in hyponatraemic rats
Treatments for hyponatraemia secondary to SIADH have different action sites\textsuperscript{1,2}

SALT-1 and SALT-2¹

- Randomised trials on tolvaptan treatment in adults (≥18 years) with chronic hypervolaemic or euvolaemic* hyponatraemia of diverse origin

- Patients distributed between aetiologies (CHF, cirrhosis, and SIADH) and severities of hyponatraemia (mild [130–134 mmol/L] and marked [<130 mmol/L])

- Oral study treatment administered once-daily as adjunct to physician-assessed standard therapy
  - Diuretics and fluid restriction allowed at physician’s discretion
  - Demeclocycline, lithium chloride or urea not allowed

2. tolvaptan Summary of Product Characteristics.
SALT-1 and SALT-2: Study design$^{1,2}$

Objective
- To evaluate the efficacy and safety of tolvaptan in patients with euvolaemic* or hypervolaemic hyponatraemia

Method
- Identical prospective, multicentre, randomised, double-blind, placebo-controlled studies in the US, Canada and Europe

2. tolvaptan Summary of Product Characteristics.
SALT-1 and SALT-2: Inclusion and exclusion criteria

Eligible patients:

• Over 18 years of age
• Non-acute hypervolaemic or euvolaemic* hyponatraemia due to heart failure, liver cirrhosis or SIADH and others
• Hyponatraemia defined as a serum [Na+]< 135 mmol/L
  – Mean serum [Na+] at study entry 129 mmol/L
• SIADH was the most common cause of hyponatraemia

Excluded patients:

• Symptomatic
• Likely to require saline therapy
• Acute and transient hyponatraemia associated with head trauma or postoperative state
• Hyponatraemia due to primary polydipsia, uncontrolled adrenal insufficiency or uncontrolled hypothyroidism were excluded

SALT-1 and SALT-2: Endpoints\textsuperscript{1,2}

Primary endpoints:
• Correction of serum [Na\textsuperscript{+}] assessed by change in average daily serum sodium concentration from:
  – Baseline to day 4 (‘short-term efficacy’)
  – Baseline to day 30 (‘sustained efficacy’)

Secondary endpoints included:
• Absolute serum [Na\textsuperscript{+}] at each visit
• Time to normalisation of the serum [Na\textsuperscript{+}]
• Percentage of patients requiring fluid restriction
• Change in baseline scores at day 30 on a patient-reported SF-12 Health Survey

\textsuperscript{2} Tolvaptan Summary of Product Characteristics.
SALT-1 and SALT-2: Absolute increase in serum [Na⁺], pooled analysis

Serum [Na⁺] according to the day of patient visit

- * p < 0.0001.
- tolvaptan: Day 0 n=214; Day 37 n=169; Placebo: Day 0 n=206; Day 37 n=151

SALT-1 and SALT-2: Primary endpoints, aetiology subsets\textsuperscript{1}

Change from baseline in serum [Na\textsuperscript{+}] in patients receiving tolvaptan or placebo\textsuperscript{1}

<table>
<thead>
<tr>
<th>Group</th>
<th>Day 4</th>
<th>Day 30</th>
</tr>
</thead>
<tbody>
<tr>
<td>SIADH</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>CHF</td>
<td>*</td>
<td>*</td>
</tr>
</tbody>
</table>

SIADH = Syndrome of Inappropriate Antidiuretic Hormone Secretion, CHF = Congestive Heart Failure

\textsuperscript{1} Data on file.

\textsuperscript{2} tolvaptan Summary of Product Characteristics.
SALT-1 and SALT-2: Primary endpoints, SIADH subgroup\textsuperscript{1}

Average daily AUC of change from baseline in serum [Na\textsuperscript{+}]\textsuperscript{1}

<table>
<thead>
<tr>
<th></th>
<th>Day 4</th>
<th>Day 30</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>a p &lt; 0.001 tolvaptan (investigator-diagnosed) vs placebo (investigator-diagnosed)</td>
<td>a p &lt; 0.001 tolvaptan (lab-diagnosed) vs placebo (lab-diagnosed)</td>
</tr>
<tr>
<td></td>
<td>b p ≤ 0.001 tolvaptan (lab-diagnosed) vs placebo (lab-diagnosed)</td>
<td></td>
</tr>
</tbody>
</table>

SALT-1 and SALT-2: Serum $[\text{Na}^+]$ normalisation at all time points, SIADH subgroup\(^1\)

Proportion of patients with normalised serum $[\text{Na}^+]$
SIADH subgroup, all time points\(^1\)

<table>
<thead>
<tr>
<th>Day</th>
<th>Placebo</th>
<th>Tolvaptan</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5.5</td>
<td>25.0 (^a)</td>
</tr>
<tr>
<td>2</td>
<td>5.2</td>
<td>33.3 (^a)</td>
</tr>
<tr>
<td>3</td>
<td>8.6</td>
<td>39.2 (^a)</td>
</tr>
<tr>
<td>4</td>
<td>11.5</td>
<td>60.0 (^a)</td>
</tr>
<tr>
<td>11</td>
<td>20.8</td>
<td>68.0 (^a)</td>
</tr>
<tr>
<td>18</td>
<td>23.4</td>
<td>66.6 (^a)</td>
</tr>
<tr>
<td>25</td>
<td>23.8</td>
<td>70.4 (^a)</td>
</tr>
<tr>
<td>30</td>
<td>26.8</td>
<td>68.0 (^a)</td>
</tr>
<tr>
<td>FU</td>
<td>25.0</td>
<td>26.3</td>
</tr>
</tbody>
</table>

BSL; Baseline. FU; 7 day follow up
\(^a\) \(p < 0.05\) tolvaptan vs placebo group

SALT-1 and SALT-2: Change in overall health status, pooled analysis

Changes in SF-12 general health survey scores after 30 days of oral administration

- Placebo (n=223)
- Tolvaptan (n=225)

<table>
<thead>
<tr>
<th></th>
<th>Physical Component Score</th>
<th>Mental Component Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>0.17</td>
<td>1.78</td>
</tr>
<tr>
<td>Tolvaptan</td>
<td>1.38</td>
<td>5.12</td>
</tr>
</tbody>
</table>

p = 0.1789
p = 0.0154

SALT-1 and SALT-2: Change in overall health status, SIADH subgroup¹

Changes in SF-12 general health survey scores after 30 days of oral administration¹

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=41)</th>
<th>Tolvaptan (n=39)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical Component Score</td>
<td>-0.16</td>
<td>3.64</td>
</tr>
<tr>
<td>Mental Component Score</td>
<td>-0.45</td>
<td>5.47</td>
</tr>
</tbody>
</table>

Changes from baseline

Treatment effects on length of hospital stay, SIADH and other¹

Length of stay in patients with severe hyponatraemia, subgroup analysis

- All patients with severe hyponatraemia (serum $[\text{Na}^+] < 130$ mmol/L) and a clinical diagnosis of SIADH plus those classified as “Other” (i.e., not meeting clinical criteria for a diagnosis of SIADH, CHF or cirrhosis)

- Post-hoc data, not powered to show length of stay

Conclusions

• Tolvaptan appears to be an effective and well tolerated therapy for hospitalised inpatients with severe hyponatraemia

• There was a significant rise in mean serum sodium levels following tolvaptan therapy

• Target level of serum sodium (>130 mmol/L) was achieved in 80% of episodes after tolvaptan therapy

• No patient developed rapid correction of sodium or osmotic demyelination syndrome as a result of tolvaptan therapy in this study

• Tolvaptan can be used for the treatment of inpatient hyponatraemia where conventional therapies have failed
Phase III, open-label, long-term extension of SALT studies\textsuperscript{1,2}

A total of 111 hyponatraemic patients (mean serum [Na\textsuperscript{+}] = 130.8 $\pm$ 4.4 mmol/L) received tolvaptan for a mean follow-up of 701 days\textsuperscript{2}

Patients received tolvaptan at an oral dose of 15, 30 or 60 mg once daily, after having returned to standard of care for at least 7 days\textsuperscript{1,2}

Serum [Na\textsuperscript{+}] improved as early as the first day after dosing and remained $> 135$ mmol/L throughout the observation period ($p < 0.001$ vs baseline at most time points)\textsuperscript{1,2}

Long-term tolvaptan treatment was well tolerated\textsuperscript{2}

\textsuperscript{1} tolvaptan Summary of Product Characteristics.
SALTWATER: SALT-1 and SALT-2 randomised controlled trials and open-label extension study¹

Serum [Na⁺] obtained in the course of the SALT-1 and -2 and SALTWATER trials

Adverse events, pooled analysis

• Adverse event profiles were comparable between tolvaptan- and placebo-treatment groups\(^1\)

• Most common adverse events associated with tolvaptan use were thirst and dry mouth\(^1\)

• Excessive rates of serum \([\text{Na}^+]\) increase were experienced in only 4 out of 223 patients (1.8%) in the tolvaptan-treated group during the first 24 hours of the study\(^1\)
  
  – Protocol-defined desired rate of correction was \(\leq 0.5\) mmol/L per hour; the maximum observed rate of sodium correction was 0.61 mmol/L per hour

Using speed of onset of hyponatraemia secondary to SIADH to guide your treatment choice

Hyponatraemia

Acute

24–48 hr

Gradual onset

> 48 hr

3% saline ± furosemide

Severe symptoms

Mild symptoms or asymptomatic

3% saline ± furosemide

Fluid restriction +/- pharmacological therapies*

*Including tolvaptan; conivaptan; demeclocycline; urea

If the speed of onset is not known, the hyponatraemia should be treated as though it is gradual onset